Tetrahedron Vol. 48, No. 10, pp. 1953-1958, 1992
Printed in Great Britain

0040-4020/92 $3.00+.00

Manganese Dioxide in a New Role of Sulfur Extrusion in thioamides†

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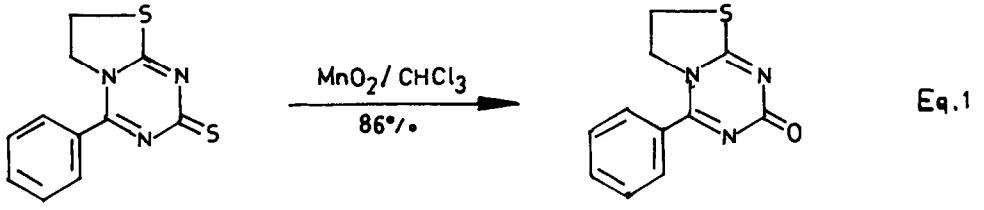
(*Received in UK* 17 *January* 1992)

Abstract: A simple and efficient procedure for the mild conversion of thioamides to amides in good yields using active manganese dioxide is described.

Diverse synthetic methods are available for the conversion of thioamides into their corresponding amides. For example, potassium t-butoxide, sodium ethoxide, sodium hydroxide with halogens under phase transfer catalysis[1], m-chloroperbenzoic acid[2], bis(p-methoxy phenyl)telluroxide[3], phase transfer catalysed method[4], trimethyloxonium salts[5], dimethyl sulfoxide with acids[6] or iodine[7], nitrosonium tetrafluoroborate[8], benzene seleninic anhydride[9], dimethyl selenoxide[10] and diarylselenoxide[11] have all been used with some degree of success. Recently, Masuda and co-workers[12] and Davis and co-workers[13] have used the trifluoro acetic anhydride and mercury (II) acetate to bring out such a transformation. However, the different reagents used for this conversion have varying degree of success as well as limitations due to side reactions. We now wish to report a reasonably simple and efficient method which enables one to economically desulfurise thioamides to their oxo analogues using active manganese dioxide in good yields.

In connection with an oxidation of fused heterocycles[14], a new method for the conversion of thioamides into amides with the use of active manganese dioxide[15] has been observed for the first time (eq. 1). This reaction is quantitative and occurs to the total exclusion of thiazoline



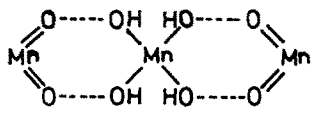
Eq.1

ring oxidation[16] as shown in eq 1. This surprising and unknown and a new behaviour of manganese dioxide appears to be interesting and a variety of thioamides were converted smoothly to the corresponding amides (Table 1).

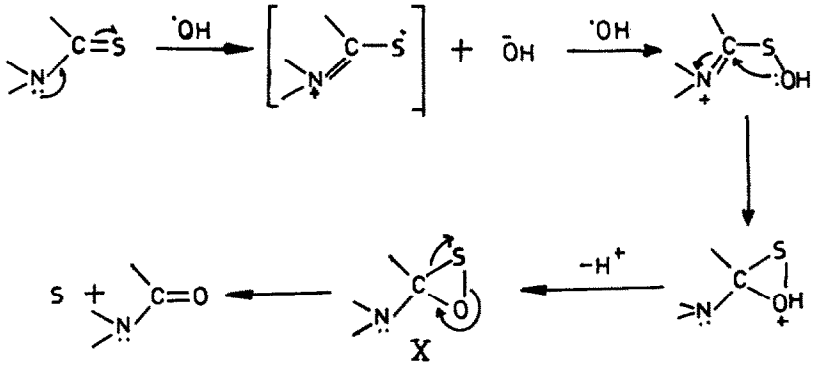
† IICT Communication No.2792.

This reaction is applicable to thioamides, thioureas, as well as thiolactams and proceeds cleanly to give the products in high yields. Primary, secondary and tertiary thioamides undergo this reaction with equal efficiency. For example, allyl urea is produced in 90% yield, caprolactam in 76% and N-methyl pyrrolidone in 88% yield. All the reactions have been done at room temperature by shaking a mixture of the oxidant (active manganese dioxide) and the substrate in chloroform for 8 to 12h while the reaction was monitored by TLC. In each case, the corresponding amides has been obtained as the end product, identified by its melting point, IR and mass spectrum. Elemental sulfur extruded in the reaction was separated during purification of the amide on column chromatography and identified by mass spectrum. In fact, tetramethyl thiourea gives 80% yield of sulfur, so that essentially one equivalent of sulfur is produced.

The structure of active manganese dioxide (I) which contains potentially labile hydroxy groups is well documented[17] on the basis of ESR and other studies. Thus, the mechanism of this new reaction can be explained by the participation of labile hydroxy radicals, to give probably a cyclic intermediate (X) that undergoes sulfur extrusion (Scheme 1). Similar results were obtained when the reaction was carried out under nitrogen atmosphere, thus eliminating the possibility of air oxidation. This further proves that the oxygenation is occuring through oxygen transfer from active manganese dioxide (I) to thione substrate. The possible mechanism for this conversion is shown in Scheme 1.



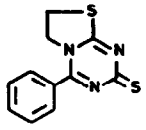
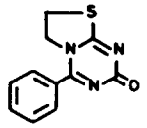
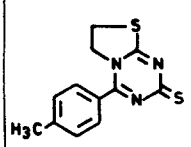
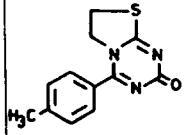
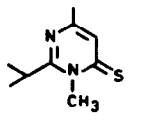
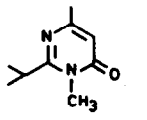
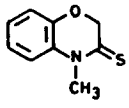
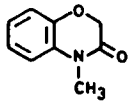
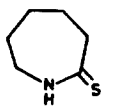
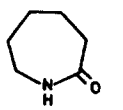
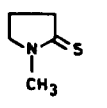
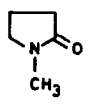
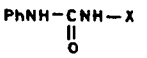
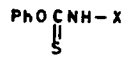
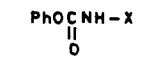
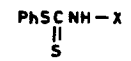
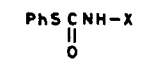
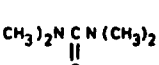
I



Scheme 1

Manganese dioxide is a well known oxidising reagent for the dehydrogenation of diverse classes of organic compounds. Although a few examples of manganese dioxide oxidation via oxygen transfer are known[18], the reaction reported in this paper is unique, in the way it displaced sulfur offering its own oxygen.

In conclusion, the mild reaction conditions, the high yields and purity of the products obtained coupled with a simple experimental procedure undoubtedly makes this method superior to some of the known methods.

Compd	THIOAMIDE	AMIDE	Yield %	mp °C	m/z	IR cm^{-1}	^1H NMR ($CDCl_3$)(δ PPM)
1.			86	247	231	1675 1555	8.43(m,2H,aromatic) 7.45(m,3H,aromatic) 4.59 (t,2H,-NCH_2),3.42(t,2H,-SCH_2)
2.			88	252	245	1675 1560	8.43(m,2H,m to -CH_3) 7.45(m,2H,o to -CH_3) 4.59 (t,3H,-NCH_2),3.43(t,2H,-SCH_2)
3.			76	B.P. 120 (8 mm)	166	1660	1.28&1.30(d, 3H,3H,isopropylmethyls) 2.21(s,3H,C-methyl),3.1(hep,1H, methineproton),3.53(s,3H-NCH_3) 6.13(s,1H,aromatic)
4			82	57	163	1675	7.02(m,4H,aromatic),3.55(s,3H, -NCH_3),4.60(s,2H,-OCH_2)
5			85	71	113	1670	3.22(t,2H,-NCH_2),2.55(t,2H,3-CH_2) 1.77(m,6H,4,5,6-CH_2 s)
6			82	B.P. 202	99	1695	3.4(t,2H,5-CH_2),2.88(s,3H,-NCH_3) 2.33(m,4H,3&4 CH_2)
7		 X = -$CH_2CH=CH_2$	77	120	176	3310 1630	7.0-7.35(m,5H,phenyl),3.80(d,2H, NH-CH_2),5.15(t,2H,CH=$\underline{CH_2}$),5.82 (m,1H,$\underline{CH}$=CH_2),5.40&8.1(s,1H, exchanged with D_2O,two-NHs)
8		 X = -CH_2-CH=CH_2	75	132	177	1640	7.01-7.46(m,5H,phenyl),3.80(d,2H, $NHCH_2$)5.15(t,2H,CH=$\underline{CH_2}$),5.82(m, 1H,$\underline{CH}$=CH_2),6.6(br,s,1H,Exch- enged with D_2O,NH)
9		 X = -CH_2-CH=CH_2	78	oily	193	1635	7.0-7.42(m,5H,phenyl),3.83(d,2H, -$NHCH_2$),5.18(t,2H,CH=$\underline{CH_2}$),5.85(m, 1H,$\underline{CH}$=CH_2),6.8(s,1H,exchanged with D_2O,-NH)
10			79	177	175	1640	2.81 (s, N-methyls)

EXPERIMENTAL

Melting points were determined in open capillaries with mettler FP-51 melting point apparatus and are uncorrected. IR spectrum ν_{max} in cm^{-1} were recorded in KBr pellets on Perkin-Elmer model 293B spectrophotometer. ^1H NMR spectra were obtained on Brucker 300 MHz or Varian FT-80A MHz instruments in $CDCl_3$ using TMS as internal standard. Mass spectra were run on VG micromass 7070H. Compounds (5 & 10) were obtained commercially from Aldrich Chem Co. Remaining substrates were synthesised as described below.

Synthesis of 6,7-dihydrothiazolo[3,2-a]-1,3,5-triazine-4-aryl-2-thione (1 & 2): The compounds 1 & 2 were synthesised by following literature procedure[14]. A representative procedure of **1** is given as follows:

To a solution of ammonium thiocyanate (0.76 g, 0.01 mol) in acetone, equimolar quantity of benzoyl chloride (1.4 g) was added dropwise with shaking. After heating the mixture on steambath for 1h equimolar quantity of 2-aminothiazoline (1.02 g) was added and refluxed for 2h. The solvent was distilled off and the residue treated with ice-cold water. The solid that separated was filtered, dried and purified on column (finer than 200 mesh) chromatography. (2.4 g, 85%), mp 251°C, m/z: 247(M^+); IR(KBr): ν_{max} 1560 and 1260 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.46-7.48 (m, 5H, phenyl), 4.71 (t, 2H,-NCH_2), 3.43 (t, 2H, -SCH_2).

Compound **2** was made according to the above method using p-methyl benzoyl chloride (1.9 g, 75%), mp 265°C, m/z: 261 (M^+); IR(KBr): ν_{max} 1560 and 1260 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.44 (m, 2H, m to CH_3), 7.48 (m, 2H, o to CH_3), 4.71 (t, 2H, -NCH_2), 3.44 (t, 2H, -SCH_2).

Compound 3: Compound N-methyl-2-isopropyl-4-methyl-pyrimidine-6-one(10 g, prepared by methylation of 2-isopropyl-4-methyl-pyrimidine-6-one with CH_3I/K_2CO_3) was mixed with P_2S_5 (10 g) in dry toluene (300 ml) and heated under reflux for 4h. Toluene was removed under vacuum, crushed ice was added to the residue and extracted with dichloromethane. The dichloromethane layer was dried over anhydrous sodium sulphate, filtered and concentrated. The residue was purified through column chromatography (finer than 200 mesh). (1.7 g, 80%), mp 91°C, m/z: 182(M^+); IR(KBr): ν_{max} 1160 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.29 & 1.39 (d, 3H, 3H, isopropyl methyls), 2.22 (s, 3H, C-CH_3), 3.28 (hep, 1H, methine proton), 4.03 (s, 3H, N-CH_3), 7.31 (s, 1H, aromatic).

Compound 4: The N-methylbenzoxazine-2-one (8.1 g, 0.05 mol) in 10% acetonitrile (50 ml) solution was treated with powdered P_2S_5 (22 g, 0.05 mol) and to this stirred suspension was added triethyl amine (4N equ) in three portions with ice water cooling to moderate the exothermic reaction. The resulting solution was left at room temperature for 24h and poured into cold water. The separated solids were filtered, dried and recrystallised from benzene. Yield (8 g, 90%), mp 78°C, m/z: 179 (M^+); IR($CHCl_3$): ν_{max} 1120 cm^{-1}; ^1H NMR($CDCl_3$): δ 3.83 (s, 3H, -NCH_3), 4.88 (s, 2H, -OCH_2); 7.07 (m, 4H, aromatic).

Compound 6: The N-methylpyrrolidine-2-one (9.69 g, 0.1 mol) and sulfur (6.4 g, 0.2 g atoms) were heated under nitrogen with stirring at 80°C. Heating was continued until the evolution

of hydrogen sulfide ceased. The resulting black mixture was distilled under reduced pressure and the volatile product was isolated and purified again by vacuum distillation. Yield (1.7 g, 15%), bp 125°C at 7.3 mm, IR ($CHCl_3$): ν_{max} 1127 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.88 (t, 2H, 3-CH_2), 2.05 (q, 2H, 4-CH_2), 3.70 (t, 2H, 5-CH_2), 3.17 (s, 3H, N-CH_3).

Compounds 7,8 & 9: The compounds 7, 8 and 9 were synthesised by the following literature procedure[19]. A representative procedure of 7 is given as follows:

Aniline (1.86 g, 0.02 mol) and allyl isothiocyanate (1.98 g, 0.02 mol) were dissolved in dry ether and 2-3 drops of triethyl amine was added. The reaction mixture was stirred at room temperature for 4h. The ether was removed and the residue was purified by column chromatography (finer than 200 mesh). Yield (3.6 g, 94%), mp 95°C, IR($CHCl_3$): ν_{max} 3340, 3160 & 1190 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.27 (q, 2H, NH-$\underline{CH_2}$), 5.15 (dd, 2H, CH-$\underline{CH_2}$), 5.82 (m, 1H, $\underline{CH}$-CH_2), 6.1 (br, 1H, $\underline{NH}$-CH_2, exchanged with D_2O), 8.34 (br, 1H, Ph-$\underline{NH}$, exchanged with D_2O), 7.18-7.41 (m, 5H, phenyl).

Compounds 8 & 9 were made according to the above method using phenol (compound 8) and thiophenol (compound 9).

General reaction procedure for the conversion of thioamides to amides using active MnO_2:

A representative procedure is illustrated for compound **6** as follows:

N-Methylpyrrolidine thione (1 g) was dissolved in 25 ml of dry chloroform under nitrogen and 4 g of active manganese dioxide was added. The reaction was stirred at room temperature and monitored by TLC. After 12h, the reaction mixture was filtered and the residue was washed thrice (3 x 15 ml) with chloroform. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, finer than 200 mesh) to obtain pure product.

Remaining compounds were also prepared in the same manner except that methanol was used to wash the residue in the case of tetramethylurea, since it is not soluble in chloroform. Except for N-methylpyrrolidinethione, all other systems were run in flasks open to air with no effect on the yields of the conversion. All reactions were conducted using four fold excess of active manganese dioxide.

Acknowledgement:

We thank Dr M Pardhasaradhi for many helpful discussions. One of us (BRR) is thankful to the CSIR, New Delhi, and Director, IICT, Hyderabad, for providing financial assistance.

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